

AMENDMENTS TO THE CLAIMS

This listing of the claims will replace, without prejudice, all prior versions, and listings, of claims in the application.

1.- 45. (cancelled)

46. (withdrawn) A composition comprising a mixture of two or more antibodies or antibody fragments, said antibodies or antibody fragments being selected from the group consisting of a native inhibitory antibody against FVIII or a fragment thereof and one or more modified antibodies or modified antibody fragments of said native antibody according to claim 34, wherein said mixture has an intermediate inhibitory activity against Factor VIII.

47. (cancelled)

48. (withdrawn) A method for treatment and prevention of thromboembolic disorders, comprising administering an effective dose of a monoclonal antibody or fragment thereof according to claim 34.

49. (withdrawn-currently amended) The method for treatment and prevention of thromboembolic disorders according to claim 48, further comprising concomitantly administering administering drug(s) inhibiting platelet aggregation.

50. (withdrawn) The method of claim 49, wherein said drug(s) inhibiting platelet aggregation, is(are) selected from the group consisting of asperin, abciximab (Rheopro^R) or an antithrombolytic agent.

51. (withdrawn) A method for obtaining a library of at least two inhibitory antibodies against factor VIII with variable maximal inhibitory activity and with substantially the same affinity, said method comprising modifying the size of an inhibitory antibody against FVIII or fragment thereof by modifying the glycosylation in the variable region of said inhibitory antibody and selecting at least one antibody or fragment for which affinity is not substantially affected.

52. (withdrawn) The method of claim 51, which method comprises the step of modifying the glycosylation in the variable region of an inhibitory antibody against FVIII or fragment thereof, and selecting those antibodies for which the affinity is not substantially affected.

53. (withdrawn) The method according to claim 51, wherein said factor VIII inhibitory antibody is directed against the C1 domain of FVIII.

54. (withdrawn) The method according to claim 51, wherein said factor VIII inhibitory antibody is Krix-1.

55. (withdrawn) A library of factor VIII inhibitory antibodies obtained by the method according to claim 51.

56. (withdrawn) The method according to claim 48, wherein said thromboembolic disorder is selected from the group consisting of deep vein thrombosis and pulmonary embolism secondary to surgical intervention, immobilization or chronic hereditary or acquired thrombophilia, and treatment of deep vein thrombosis, pulmonary embolism, stroke, atrial fibrillation, non Q wave myocardial infarct, non ST elevated myocardial infarct, unstable angina, sepsis or SIRS.

57. (withdrawn) A method for treatment and prevention of thromboembolic disorders, comprising administering an effective dose of the composition according to claim 46.

58. (currently amended) The An inhibitory antibody against Factor VIII or a fragment thereof according to claim 34 comprising an immunoglobulin light chain sequence having at least 90% sequence similarity to represented by SEQ ID NO:4, and comprising an immunoglobulin heavy chain amino acid sequence having at least 90% sequence similarity to represented by SEQ ID NO:2, wherein the glycosylation site at positions Asn47 to and/or Thr49 of SEQ ID NO:2 is mutated, or wherein position Asn47 of SEQ ID NO:2 is deglycosylated.

59. (previously presented) The antibody or fragment thereof according to claim 58 wherein said glycosylation site is mutated by changing Asn47 to Gln47, Asn47 to Glu47, Asn47 to Asp47 and/or by changing Thr49 to Ala49.

60. (previously presented) The antibody or fragment thereof according to claim 58 wherein said glycosylation site is mutated by changing Asn47 to Gln47.

61. – 63. (cancelled)

64. (currently amended) The An inhibitory antibody against Factor VIII or a fragment thereof according to claim 34 comprising an immunoglobulin variable light chain comprising the CDR1, CDR2, and CDR3 sequences regions depicted in SEQ ID NO:36, SEQ ID NO:37, and SEQ ID NO:38 respectively, and comprising an immunoglobulin variable heavy chain comprising the CDR1, CDR2, and CDR3 sequences with regions depicted in SEQ ID NO:33, SEQ ID NO:34, and SEQ ID NO:35, respectively, wherein

the glycosylation site at positions 3 to and/or 5 in the CDR1 region of the immunoglobulin variable heavy side chain comprising the sequence of SEQ ID NO:33 is mutated, or wherein Asn at position 3 in the CDR1 region of the variable heavy chain comprising the sequence of SEQ ID NO:33 is deglycosylated.

65. (currently amended) The antibody or fragment thereof according to claim 64, wherein the mutation is the change of Asn into Gln, Glu or Asp at position 3 in the CDR1 region of the immunoglobulin variable heavy side chain with comprising the sequence of SEQ ID NO:33 and/or wherein the mutation is the change of Thr into Ala at position 5 in the CDR1 region of the immunoglobulin variable heavy side chain comprising the sequence of SEQ ID NO:33.
66. (new) An inhibitory antibody against FVIII or a fragment thereof comprising an immunoglobulin variable heavy chain comprising the CDR1, CDR2, and CDR3 regions comprising the sequence of SEQ ID NO:33, SEQ ID NO:34, and SEQ ID NO:35, respectively, wherein the glycosylation site at positions 3 and/or 5 of the CDR1 region comprising the sequence of SEQ ID NO:33 is mutated, or wherein Asn at position 3 in the CDR1 region comprising the sequence of SEQ ID NO:33 is deglycosylated.
67. (new) The fragment according to claim 58, which is an scFv fragment represented by SEQ ID NO:26.
68. (new) The fragment according to claim 64, which is an scFv fragment represented by SEQ ID NO:26.
69. (new) The fragment according to claim 66, which is an scFv fragment represented by SEQ ID NO:26.

70. (new) A pharmaceutical composition comprising the inhibitory antibody or fragment thereof according to claim 58.

71. (new) A pharmaceutical composition comprising the inhibitory antibody or fragment thereof according to claim 64.

72. (new) A pharmaceutical composition comprising the inhibitory antibody or fragment thereof according to claim 66.

73. (new) An antibody or antigen binding fragment thereof which is a modified antibody or modified fragment of an inhibitory antibody against FVIII,
wherein the unmodified inhibitory antibody comprises as CDR1, CDR2 and CDR3 regions of the immunoglobulin variable heavy chain an amino acid sequence represented by SEQ ID NOS:33, 34, and, 35, respectively, and comprises as CDR1, CDR2, and CDR3 regions of the immunoglobulin variable light chain an amino acid sequence represented by SEQ ID NOS:36, 37, and 38, respectively, and wherein the unmodified antibody or antigen binding fragment thereof is obtainable by expression in a human lymphoblastoid cell line,
wherein the modification is a deglycosylation at position 3 in the CDR1 region of the immunoglobulin variable heavy chain comprising the sequence of SEQ ID NO:33.